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The impact of influenza vaccination on infection, hospitalisation and mortality in the Netherlands between 2003 and 2015

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ABSTRACT

Influenza epidemics annually cause substantial morbidity and mortality. For this reason, vaccination is offered yearly to persons with an elevated risk for complications. Assessments of the impact of vaccination are, however, hampered by year-to-year variation in epidemic size and vaccine effectiveness.

We estimate the impact of the current vaccination programme comparing simulations with vaccination to counterfactual simulations without vaccination. The simulations rely on an age- and risk-structured transmission model that tracks the build-up and loss of immunity over successive seasons, and that allows the vaccine match to vary between seasons. The model parameters are estimated with a particle Monte Carlo method and approximate Bayesian computation, using epidemiological data on vaccine effectiveness and epidemic size in the Netherlands over a period of 11 years.

The number of infections, hospitalisations and deaths vary greatly between years because waning of immunity and vaccine match may differ every season, which is in line with observed variation in influenza epidemic sizes. At an overall coverage of 21%, vaccination has averted on average 13% (7.2–19%, 95% range) of infections, 24% (16–36%) of hospitalisations, and 35% (16–50%) of deaths. This suggests that vaccination is mainly effective in protecting vaccinees from infection rather than reducing transmission. As the Dutch population continues to grow and age, the vaccination programme is projected (up to 2025) to gain in impact, despite a decreasing infection attack rate.

1. Introduction

Influenza epidemics are the cause of a considerable number of hospitalisations and deaths (World Health Organization, 2016; Thompson et al., 2009; Iuliano et al., 2018). In the Netherlands, it has been estimated in a comparative analysis of infectious diseases that the disease burden of influenza is second only to pneumococcal disease (Van Lier et al., 2016). Therefore, to reduce morbidity and mortality from influenza virus infection, a free-of-charge vaccination is offered yearly to risk groups. These groups comprise children and adults with a high risk of complications, and all persons over 60 years of age. In the Netherlands and other high-income countries, the number of vaccine doses required for the vaccination programme is expected to increase over the next decade due to population growth and ageing.

An important step towards evaluating the impact of influenza vaccination programmes is to determine how many infections, hospitalisations and deaths are averted by vaccination. Such estimates are available for the USA (Kostova et al., 2013; Foppa et al., 2015; Jackson et al., 2015), assuming that incidence is inversely proportional to the effective vaccination coverage. However, this method underestimates the true number of averted infections as it disregards the indirect effects of vaccination. To include these indirect effects a dynamic transmission model is required. Furthermore, such a model for seasonal influenza should capture the variation between seasons, as infections that occurred in previous seasons may affect subsequent seasons (Woolthuis et al., 2017). The variation between influenza seasons is largely caused by the genetic drift of the influenza virus resulting in antigenic change (Smith et al., 2004; Bedford et al., 2014). Previously infected individuals lose their immunity over the years, as the circulating virus strain less and less resembles the virus strain that caused the initial infection (Pease, 1987). As the antigenic drift can vary from season to season, the rate at which naturally infected persons lose protection to the circulating strain also varies. Henceforth, this rate will be called the waning immunity rate, not to be confused with the waning of natural

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immunity. Variations in antigenic drift also lead to variations in how well the vaccine matches the circulating strain. Both the varying waning immunity rate and vaccine match result in variations in the number of infections that occur during the subsequent influenza season. The newly infected persons add to the population of previously infected people that are still immune, setting a different stage for the next season when the waning immunity rate and vaccine match may be different again. Many dynamic models (Vynnycky et al., 2008; Pitman et al., 2012; Rose et al., 2014; Gerlier et al., 2017) include this build-up and loss of immunity over seasons, but the waning immunity rate is assumed to be fixed, leading to identical influenza seasons in simulations. Other transmission models (Baguelin et al., 2013, 2015) consider isolated influenza seasons, that do capture the seasonal variation but lack the connection with the subsequent season.

We develop a stochastic transmission model, linking the season-to-season dynamics and including variable loss of immunity, similar to Woolthuis et al. (2017), to estimate how many infections, hospitalisations and deaths are prevented by the current vaccination programme in the Netherlands. To this end, we first estimate the infection attack rates and vaccine effectiveness in the Netherlands, based on surveillance data, virology data, and literature. Subsequently, the distributions of infection attack rate and vaccine effectiveness are used to parameterise the transmission model. Using counterfactual simulations without vaccination, the number of averted infections, hospitalisations and deaths is estimated, in absolute numbers, as a fraction, and per vaccine dose. Finally, it is assessed how these results are affected by an evolving demography.

2. Methods

We infer the fraction of the population that is infected during an influenza season from multiple information sources, similar to the work of McDonald et al. (2014). The main data source is the sentinel practices of NIVEL Primary Care Database that contains information on the occurrence of influenza like illness (ILI) as reported by sentinel general practitioners (GPs), stratified in 19 age groups. As not all of these patients are infected with influenza virus, a sample of ILI patients is tested for influenza yielding the fraction of influenza virus infected ILI patients per age group and season. On the other hand, not all people infected with influenza virus develop ILI (Carrat et al., 2008), and when they do, the youngest and oldest age groups are more likely to visit their GP (Friesema et al., 2009). All these fractions and probabilities taken together, lead to an infection attack rate distribution based on data of 11 influenza seasons from 2003/2004 to 2014/2015 (with the exception of the pandemic season 2009/2010). The vaccine effectiveness also differs from season to season. By combining published vaccine effectiveness values for 3 subtypes (Belongia et al., 2016) with the subtype distribution over the 11 influenza seasons (Van Doorn et al., 2017), we construct a vaccine effectiveness distribution for a “composite strain”. We do not distinguish between subtypes, but we model a general influenza strain that leads to a typical infection attack rate (described by the inferred distribution), and against which a trivalent vaccine has a typical vaccine effectiveness (described by the inferred distribution). See SI section 1 for details on the inference procedure.

As we are interested in the number of infections, hospitalisations and deaths over the entire season, we use time steps of 1 year. This allows for the use of final size calculations and for disregarding seasonality. Each year, the structured compartmental model passes through different stages of a cycle (Fig. 1) to simulate the infection attack rate and vaccine effectiveness of that year. These outcome measures over several years are compared to the inferred distributions of infection attack rate and vaccine effectiveness, to estimate the model parameters.

Most model parameters are known or estimated from different sources (see SI section 3). For the demographic composition, data from 2015 is used (Statistics Netherlands, 2014). The population is distributed over 2 risk classes (Tacken et al., 2014): persons at medical risk of complications are categorized as “high risk” and the remainder of the population falls in the “low risk” category (Fig. 2). All persons in the high risk category and/or over 60 years old are invited for yearly vaccination. Vaccination coverage (Tacken et al., 2014) in general increases with age, and risk status. Overall, 21% of the total population is vaccinated annually, 75% of which are persons of 60 years and older. The vaccine take, i.e. the probability that a vaccinated person develops an antibody response, decreases with age from 100% down to 30% for the highest age class, estimated from observed seroconversion rates in

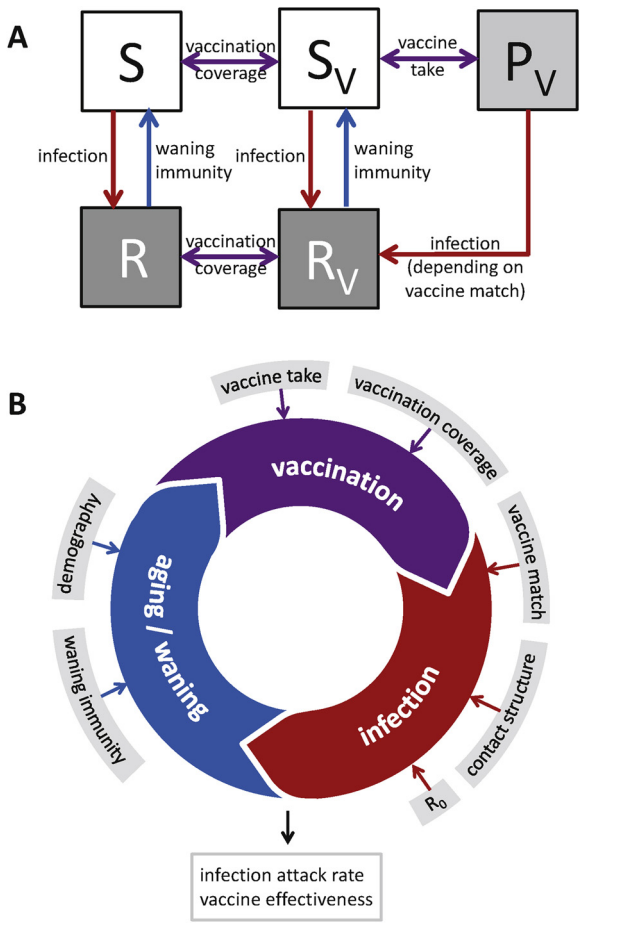

Fig. 1. Schematic overview of the influenza model. (A) Compartmental model for discrete time steps of 1 year, with classification according to vaccination and infection status: susceptible (S and S_V), immune through natural infection (R and R_V), and partially protected by vaccination (P_V), where subscript V denotes a vaccinated compartment. The model lacks an explicit infectious compartment because of the use of final size calculations. Each compartment is subdivided in 100 age classes (from 0 to 99 years of age), 2 risk groups (low and high) and 2 sexes (male and female). (B) Simulation cycle for each season consists of 3 stages. At the start of the season, people are vaccinated according to the vaccination coverage of their risk and age class, but whether they develop an antibody response is captured by the vaccine take. During the season, infection is mainly determined by the basic reproduction number R_0 and the contact structure between age and sex classes; how well vaccinated persons in the P_V compartment are protected against infection depends on the vaccine match. At the end of the season, the population ages by 1 year and the immunity of some previously infected people wanes. Vaccinated individuals return to an unvaccinated status as vaccine protection is assumed to last one season. Outcome measures are the infection attack rate and vaccine effectiveness of that season. The outer ring shows the model parameters (that can be structured by age, risk group and/or sex): demographic composition (age, risk, sex), vaccination coverage (age, risk), vaccine take (age), contact matrix (age, sex), reproduction number R_0 (scalar), waning immunity rate (2 parameter distribution), and vaccine match (2 parameter distribution). See SI section 2 for model details.

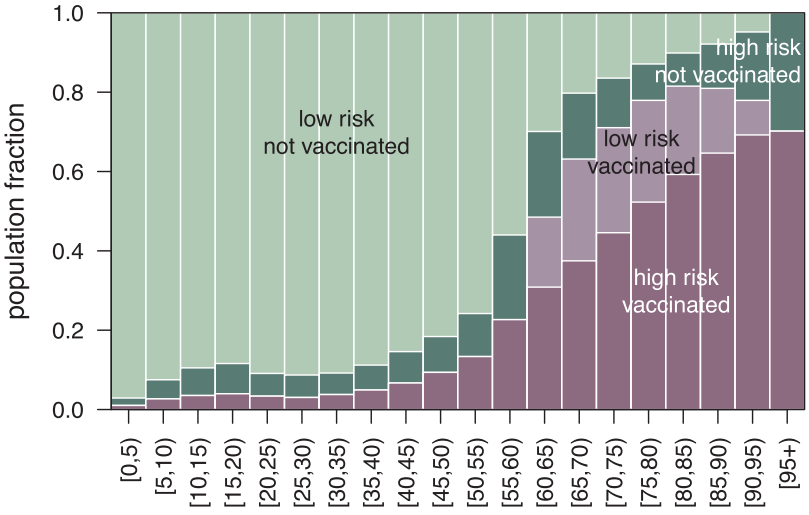

Fig. 2. Distribution of risk classes and vaccination coverage by age group (Tacken et al., 2014). The population consists of low-risk (light colours) and high-risk (dark colours) individuals. Indications to vaccinate are either medical risk of complications (high risk) and/or age over 60 years. Of these indicated individuals, a part chooses to be vaccinated (purple) and the remainder will not be vaccinated (green). See SI section 3 for tabular data.

different age groups (Goodwin et al., 2006). The contact matrix quantifies how individuals tend to mix most with similarly aged individuals, and how children and young adults have the highest contact rates (Van de Kassteele et al., 2017).

The remaining parameters, i.e. the basic reproduction number R_0, waning immunity rate, and vaccine match (between 0 and 1), are fitted to the inferred infection attack rate and vaccine effectiveness distributions. For parameter estimation, we use Approximate Bayesian Computation combined with a particle Monte Carlo method that minimizes the number of simulations (Lenormand et al., 2013). The prior distribution for the basic reproduction number is fairly informative, with a mean value of 1.8 (1.2–2.8, 95% range). In contrast to the reproduction number, the waning immunity rate and the vaccine match vary from season to season, and are identical for all age and risk groups. Both are modelled as logitnormal distributions, each with two parameters that have uniform prior distributions. The particles that represent a sample from the posterior distribution, will be used for counterfactual and forward simulations. See SI section 4 for details on the parameter estimation.

The probability of hospitalisation and death after infection depends strongly on the age and risk group of the infected person. McDonald et al. (2018) reported mortality rates for 6 elderly age classes of 60 years and older in the Netherlands. As these data do not distinguish between risk groups, we will use the distribution over the risk classes of reported influenza mortality rates in the United Kingdom (Cromer et al., 2014). This latter study defines risk groups as “at medical risk” (corresponding to our high-risk group) and “not at medical risk” (corresponding to our low-risk group). The Dutch mortality rates above 60 years of age are multiplied with the fraction of influenza deaths occurring in the hospital (Matias et al., 2016), and divided by the mortality rate per hospitalisation (Cromer et al., 2014) to arrive at the hospitalisation rates above 60 years of age. For mortality and hospitalisation rates under 60 years of age, we adopt the results of Cromer et al. (2014). To estimate the probability of hospitalisation and mortality after infection, all rates are divided by the group-specific infection attack rate from our simulation results. All rates are modelled as normal distributions.

Using the estimated parameters, influenza seasons are simulated under the current vaccination programme. Each of the 1000 simulations yields the infection attack rate, the number of hospitalisations and the number of deaths in a season. To assess the effect of the vaccination, the simulations are repeated without vaccination. The difference yields the number of infections, hospitalisations and deaths averted by vaccination. To study how these results are affected by changing demographics, the model is simulated forward in time from 2015 to 2025.

Several model and parameter choices might affect the results. We conduct a sensitivity analysis to investigate the robustness of three crucial choices. First, we study the effect of the vaccine mechanism, viz. an all-or-nothing vaccine (vaccine provides full protection to part of the vaccinees) and a leaky vaccine (vaccine provides partial protection to all vaccinees). The vaccine mechanism in our model lies in between these two extremes. Secondly, we assumed consistent vaccination where people with a vaccination indication persist in their choice whether or not to be vaccinated. This is contrasted with random vaccination where people are randomly selected for vaccination each year. And finally, the choice of prior distribution for the basic reproduction number is evaluated. See SI section 5 for details on the sensitivity analysis.

3. Results

3.1. Infection attack rate and vaccine effectiveness

The estimated overall infection attack rate shows a large between-season variability, with median infection attack rates ranging from 3 to 17 percent (Fig. 3). Taking these seasons to be representative for the Dutch situation, we use the aggregated distribution over all seasons with a median of 6.7% (2.6–17, 95% range) for parameter estimation. We excluded the pandemic year 2009/2010, but inclusion of that season would yield a similar infection attack rate of 6.9% (2.6–17), demonstrating it was not an exceptional year in terms of the infection attack rate.

To obtain the vaccine effectiveness distribution, the subtype distribution over the seasons is combined with the reported vaccine effectiveness per subtype, yielding an overall vaccine effectiveness of 45% (19–66). This is also an appropriate distribution for the Netherlands, as the same estimation procedure for vaccine effectiveness values reported for the Netherlands (Darvishian et al., 2017) leads to an average overall vaccine effectiveness of 43% (8.8% minimum to 68% maximum). More information on the results of both infection attack rate and vaccine effectiveness is provided in SI, section 1.

3.2. Parameter estimates

The parameter estimation procedure aims to match the simulated distributions of infection attack rate and vaccine effectiveness to the inferred distributions. The set of posterior particles reproduces the vaccine effectiveness distribution well, yielding a median of 45% (18–68, 95% range). The simulated infection attack rate of 6.9% (0–14) reproduces the median well, although the distribution is less skewed than inferred. Moreover, the autocorrelation of the simulated time series of attack rates resembles the autocorrelation of the observed time

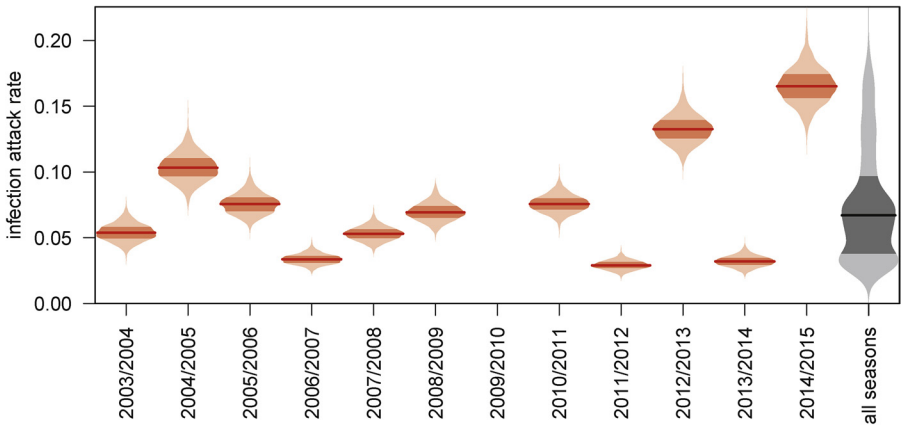

Fig. 3. Inferred infection attack rate in the Netherlands for influenza seasons from 2003/2004 to 2014/2015 with the exception of the pandemic season 2009/2010, based on the sentinel practices and virology results. Violin plots show density with interquartile range (dark area) and median value (dark line) for separate seasons (red) and all seasons aggregated (grey).

series. This shows that the interseasonal dynamics are reproduced where large and small epidemics can alternate because of the immunity propagation from one season to the next (SI section 4).

The posterior distribution of the reproduction number R_0 is 1.8 (1.3–2.7, median and 95% credible interval) which is largely determined by the informative prior distribution. The average waning rate is 0.19 (0.12–0.35) year^{-1} with a standard deviation of 0.031 (0.011–0.067) year^{-1}. Taking the reciprocal of the waning rate, an infected individual loses his immunity relative to the circulating strain after 5.1 (2.9–8.2) years on average. The vaccine match is on average 0.56 (0.49–0.66) with a standard deviation of 0.11 (0.078–0.14). As expected, parameter estimates are highly correlated (Fig. 4). Specifically, the reproduction number and waning rate are reciprocally related. The vaccine match is positively correlated with the reproduction number, although this seems specific for consistent vaccination (see SI section 5).

The probabilities of hospitalisation and mortality after influenza infection are calculated (Table 1) from the reported hospitalisation and mortality rates (McDonald et al., 2018; Cromer et al., 2014) and our infection attack rate results. Hospitalisation is highest in the very young and elderly, while influenza mortality mainly occurs in elderly. High risk persons have higher probabilities of hospitalisation and mortality than similarly aged persons at low risk.

3.3. Number of averted infections, hospitalisations and deaths

Using the posterior parameter sets, the situation of 2015 is simulated with and without vaccination. Results are reported as mean values with the 95% range between brackets. The infection attack rate under the current vaccination programme of 6.9% (0–14) would increase to 8.0% (0–14) if no one were vaccinated (Fig. 5), implying mean that 13% (7.2–19) of the infections are averted per year. Most infections are averted in the older age groups of 60 years and older, which have the highest proportion of vaccinated persons.

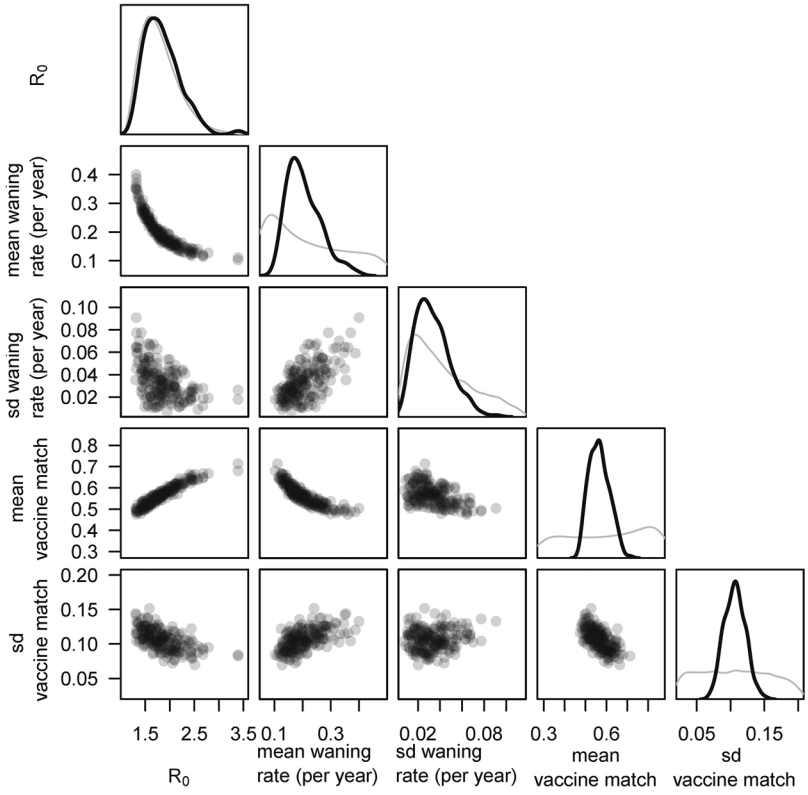

Fig. 4. Posterior distributions of the reproduction number R_0, waning rate (mean and standard deviation) and vaccine match (mean and standard deviation). Density plots (on-diagonal) show posterior (black line) and prior distribution (grey line). Scatter plots (off-diagonal) show pairwise relations.

Table 1
Probability distributions of hospitalisation p(hosp|infected) and mortality p(mort|infected) conditioned on infection, per risk and age group, of which mean and (standard deviation) are reported here. These probabilities are based on mortality rates for age groups under (Cromer et al., 2014) and over (McDonald et al., 2018) 60 years of age, the fraction of influenza deaths occurring in the hospital (Matias et al., 2016), the mortality rate per hospitalisation (Cromer et al., 2014), and the infection attack rate (inferred).

Age group (years)	p(hosp|infected) × 10^3				p(mort|infected) × 10^3			
	Low risk		High risk		Low risk		High risk	
0–4	21	(1.4)	21	(1.3)	0.0090	(0.00059)	0.36	(0.021)
5–14	0.87	(0.067)	5.6	(0.3)	0.00037	(0.000029)	0.096	(0.0050)
15–44	1.1	(0.039)	6.4	(0.26)	0.0070	(0.00024)	0.26	(0.010)
45–59	1.7	(0.051)	11	(0.46)	0.014	(0.00042)	0.56	(0.024)
60–64	3	(0.099)	9.5	(0.37)	0.084	(0.0037)	2.8	(0.12)
65–69	4.3	(0.15)	8.4	(0.29)	1.2	(0.042)	5.5	(0.19)
70–74	8	(0.18)	16	(0.35)	2.3	(0.050)	10	(0.23)
75–79	14	(0.5)	27	(0.99)	5.1	(0.19)	23	(0.86)
80–84	38	(1.3)	75	(2.5)	14	(0.48)	64	(2.2)
85–99	93	(2)	180	(3.8)	35	(0.74)	160	(3.3)

From the simulated infection attack rates in each age and risk group, the numbers of hospitalisations and deaths are calculated using the hospitalisation and mortality probabilities in Table 1. It is estimated that with vaccination 389 (8–799) persons per million are hospitalised yearly due to influenza complications. Vaccination averts 24% (16–36) of the hospitalisations, mostly in the older age classes. The many hospitalisations in the youngest age group are unaffected by vaccination, as most of these occur in unvaccinated low-risk children.

Yearly, 122 (2–263) influenza deaths per million are expected under the current vaccination programme. The majority (97%) of deaths occurs in the age groups of 60 years and older. As these groups have the highest vaccination coverage and the highest mortality probability after infection, it is not surprising that the current vaccination programme is most effective in averting deaths: 35% (16–50) of the deaths are averted by vaccination.

The current vaccination programme requires 3.56 million vaccine

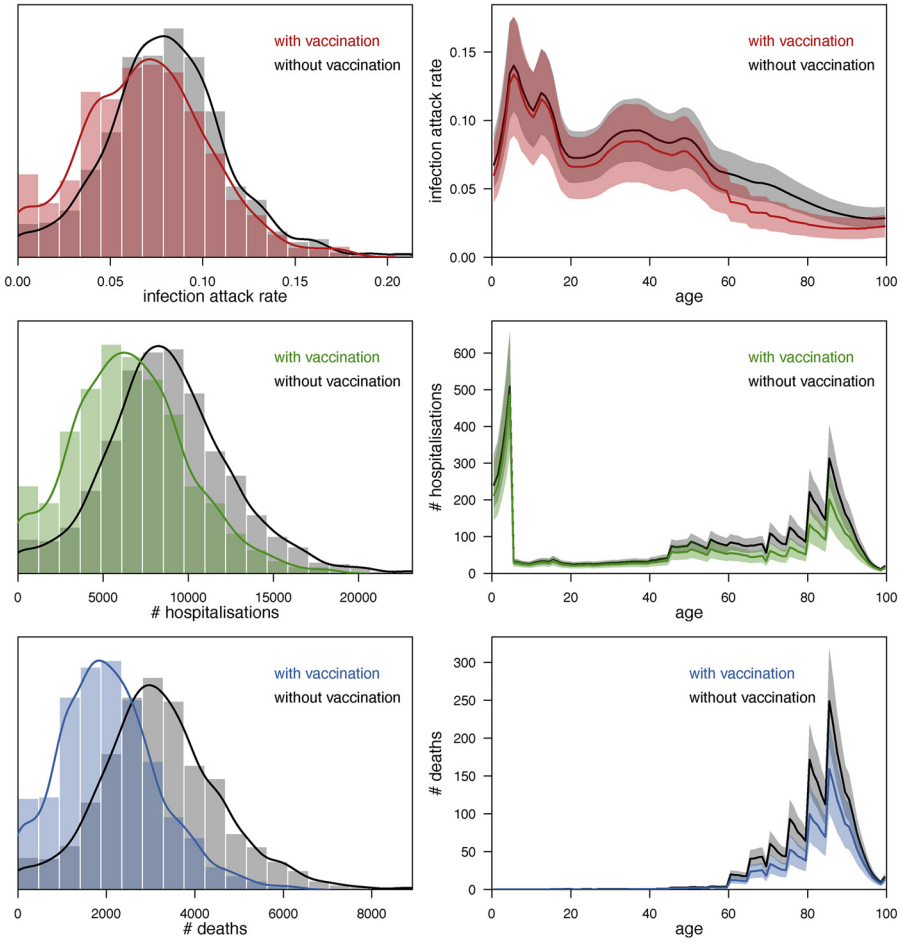

Fig. 5. Results of 1000 simulations for the 2015 situation, comparing the number of influenza infections (top), hospitalisations (middle) and deaths (bottom) per influenza season for the current vaccination programme (colours) and a scenario without vaccination (grey tones). Left-hand panels show the overall distribution as a histogram (bars) and density plot (line). Right-hand panels show the age distributions with median (line) and interquartile range (light area). Results per 5-year age group and risk group are provided in SI section 6.

Table 2
Simulated results for 2015 and 2025 under the current vaccination programme in the Netherlands. Mean values and 95% range between brackets.

	2015		2025	
	Mean	(95%)	Mean	(95%)
Population size	16.9×10^6		17.5×10^6	
Vaccine doses	3.56×10^6		4.22×10^6	
Infection attack rate	0.0689	(0–0.137)	0.0612	(0–0.128)
Total number of				
Infections	1.17×10^6	(25.9×10^3–2.32×10^6)	1.07×10^6	(0–2.25×10^6)
Hospitalisations	6572	(132–13506)	6906	(0–14875)
Deaths	2058	(39–4443)	2473	(0–5528)
Averted by vaccination (%)				
Infections	13	(7.2–19)	15	(8.2–27)
Hospitalisations	24	(16–36)	27	(13–35)
Deaths	35	(16–50)	37	(15–52)
Averted per 1000 vaccine doses				
Infections	50	(27–72)	47	(25–82)
Hospitalisations	0.59	(0.38–0.89)	0.61	(0.30–0.78)
Deaths	0.31	(0.14–0.44)	0.34	(0.14–0.48)

doses for the 2015 population. Per 1000 vaccine doses 50 (27–72) infections, 0.59 (0.38–0.89) hospitalisations and 0.31 (0.14–0.44) deaths are averted.

3.4. Projections of vaccination programme impact

In the period 2015-2025, the total population is expected to increase by 4% in The Netherlands (Statistics Netherlands, 2014). In the same period, the fraction of persons of 60 years of age and older increases from 24% to 29%. Assuming constant vaccination coverage per age and risk group, the overall vaccination coverage would increase from 21% to 24%, requiring 18% more vaccine doses.

The effects of these demographic changes are studied by simulating the model forward in time (Table 2). The infection attack rate is projected to decrease in an ageing population. The reason is that children in school ages are considered to be the drivers of influenza transmission, while older age groups play a minor role (Worby et al., 2015). In the same period however, the population increases in size. As a result, the total number of influenza infections decreases only slightly. The number of hospitalisations is approximately constant, while the number of deaths increases, as these mainly occur in the growing elderly population.

Combined with the scenario without vaccination, the numbers of averted infections, hospitalisations and deaths are calculated. For most outcomes, the percentages averted and the numbers averted per 1000 vaccine doses, are expected to increase. This is partly caused by the higher fraction of older age groups leading to a larger role in the transmission, and partly by the higher vaccination coverage leading to additional indirect effects.

3.5. Sensitivity analysis

The full analysis – consisting of parameter estimation, determining hospitalisation and mortality probabilities, and simulations with and without vaccination – is repeated for each model in the sensitivity analysis (see SI section 5). We compare the number of averted infections, hospitalisations and deaths per 1000 vaccine doses (Fig. 6). The three models that differ in vaccine mechanism (default, all-or-nothing and leaky) yield similar outcomes, possibly because differences would only manifest at higher effective reproduction numbers. For random vaccination the impact of the vaccination programme is around 25% lower than for consistent vaccination. The reason is that random vaccination leads to a lower estimated vaccine match, which is ultimately caused by vaccine doses being squandered to persons that are already immune due to natural infection. Consistent vaccination however more closely resembles actual vaccination behaviour. With a mean prior for the reproduction number of 1.6 and 2.0, the vaccination programme impact is estimated to be slightly higher and lower, respectively, than with the default mean prior of 1.8. In all cases – except for the random vaccination model – the estimated interquartile and 95% ranges largely overlap.

4. Discussion

To evaluate the impact of seasonal vaccination in terms of the number of averted infections, hospitalisations, and deaths, we developed an influenza transmission model. The main strength of the model is the combination of indirect effects, season-to-season linkage, and variation between influenza seasons, that together comprise a biologically plausible mechanism to describe influenza dynamics (Woolthuis et al., 2017). The interseasonal variation and the parameter uncertainty lead to estimated numbers of infections, hospitalisations and deaths that vary from year to year, in line with the intrinsic variation of influenza seasons. To assess the impact of influenza vaccination, we evaluated counterfactual scenarios without vaccination. Essential to this analysis, is the build-up and loss of immunity from one season to the next. Without it, the immune fractions at the start of the season have to be estimated for every age group. However, we cannot use these estimates for the counterfactual scenario without vaccination, because we expect the natural immunity levels in the population to be higher without vaccination. By linking the seasons, the immunity propagation and subsequent waning do lead to higher immune fractions (SI section 7). Also the distinction between age and risk groups that differ in both the risk of complications and vaccination coverage, is important to evaluate the vaccination impact as accurately as possible.

We found that influenza vaccination at a coverage of 21% of the total population, averts on average 13% of infections, 24% of hospitalisations, and 35% of deaths. In the US the same ranking is observed: on average 10.2% of cases, 13% of hospitalisations, and 22% of deaths may be averted by vaccination (Kostova et al., 2013; Foppa et al., 2015). As the vaccination coverage in the US is even higher than in the Netherlands, these lower averted fractions are presumably caused by ignoring indirect effects of vaccination in the US studies. In Germany, two studies that do take the indirect effects into account, show different results. Eichner et al. (2014) report that 37% of infections are averted by vaccination, while Weidemann et al. (2017) find that only 8.6% of influenza-attributable medically attended acute respiratory infections are averted. As they use different models and different parameter estimation procedures, it is difficult to pinpoint what causes the large gap between their results or the difference with our results. Studies from the UK show vaccination effects that are very similar to our results: they find 15% of infections, 26% of hospitalisations, and 37% of deaths are

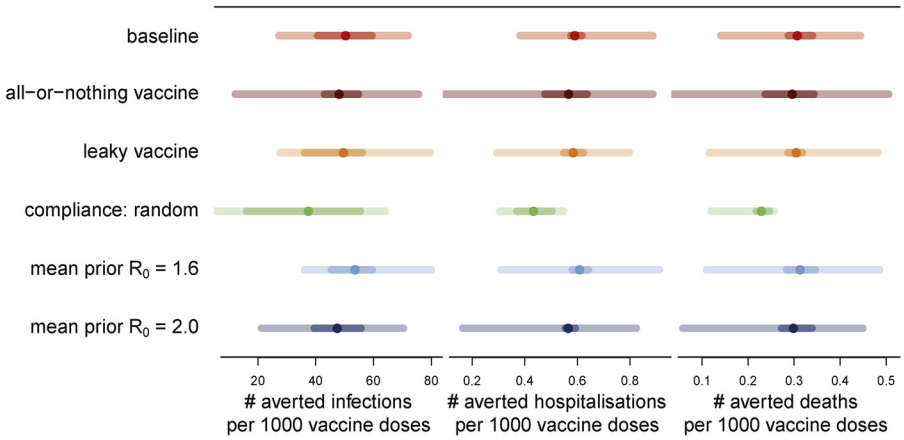

Fig. 6. Results of sensitivity analyses, comparing the number of averted infections, hospitalisations and deaths per 1000 vaccine doses for the baseline model (red), a model with an all-or-nothing vaccine (dark red), a model with a leaky vaccine (orange), a model with random vaccination (green), the default model with a mean prior reproduction number of 1.6 (light blue) and 2.0 (dark blue). Shown are mean (dark point), interquartile range (dark line) and 95% range (light line).

averted by the current vaccination programme, using a model based on isolated seasons (Baguelin et al., 2013, 2015). The results per vaccine dose however, are different. The first UK study (Baguelin et al., 2013) reports 0.39 averted infection per vaccine dose, versus 0.050 in this study. This discrepancy is caused by the higher infection attack rate of 25% in the study of Baguelin et al. (2013), versus 6.9% in the current analysis. The same study reports 1.74 averted deaths per 1000 vaccine doses due to generous mortality estimates by Hardelid et al. (2013), while the later UK study (Baguelin et al., 2015) uses the estimates by Cromer et al. (2014) for influenza deaths in the hospital, yielding 0.16 averted deaths per 1000 vaccine doses. Our estimate of 0.31 averted deaths per 1000 vaccine doses are based on Dutch estimates (McDonald et al., 2018) that also include mortality outside the hospital.

The average annual number of influenza deaths under the current vaccination programme in the Netherlands is estimated to be 2058 (39–4443). This is in line with previously reported average estimates of 2704 by Van Asten et al. (2012) and 1956 by Van den Wijngaard et al. (2012), and also the age distribution is well reproduced. It should be noted though that these estimates as well as those by McDonald et al. (2018) are based on all-cause mortality. Analyses using all-cause mortality may falsely attribute some deaths to influenza, whereas analyses using death records with a respiratory underlying cause may miss influenza deaths (Dushoff et al., 2006; Simonsen and Viboud, 2012). We assumed that mortality rates in the different risk groups is similar in England and the Netherlands, as well as mortality below 60 years and hospitalisation, due to lack of appropriate Dutch data. We believe that both countries are comparable in terms of risk groups and vaccination coverage.

For parameter estimation, some prior information was required due to the interdependency between the reproduction number R_0 and the waning rate. We chose an informative prior for R_0 for which independent estimates exist rather than assuming a waning rate without conclusive data. In this way, we were able to estimate an average waning immunity period of 5.1 (2.9–8.2, 95% CI) years. Only two other studies also estimate the waning immunity. Thommes et al. (2014) find a lower value of 2.95 years for influenza A and a higher value of 15 years for influenza B. For a general influenza strain, Goeyvaerts et al. (2015) report values of 2.3–3.1 years, but they assume vaccine protection lasts as long as natural immunity. We have assumed the vaccine provides partial protection during one influenza season. Estimates that are based on seroconversion rates after vaccination, are 0.8 years (Rose et al., 2014) and 1.8 years (Eichner et al., 2014). Even if vaccine protection were to last longer than one season, the effect is not expected to be large because most vaccinees were already vaccinated the year before, according to our assumption of consistent vaccination.

We have assumed one generic influenza strain instead of modelling specific strains and subtypes, similar to Goeyvaerts et al. (2015). As a result, the infection attack rates from simulations have a narrower and less skewed distribution, and show stronger autocorrelation between seasons than observed (SI section 4). With sufficient data, an analysis that distinguishes between influenza strains and subtypes could improve the current analyses, but would also require assumptions on competitive exclusion. But even with one generic strain, linking the seasons and allowing for between-season variability is in our opinion a step forward in influenza transmission modelling. Further progress could be made by including the effect of immunity on virus evolution (Kucharski and Baguelin, 2017), changes in contact structure (Luca et al., 2018), superspreading (Lloyd-Smith et al., 2005), or spatial transmission (Gog et al., 2014), that could modulate the results.

A limitation of the model is that age distributions of the number of infections, hospitalisations and deaths are nearly fixed. First, the transmission between age groups is dictated by a contact matrix; secondly, the age effect of vaccination is absorbed in a (constant) vaccine take; thirdly, the probabilities of hospitalisation and mortality are fixed per age and risk group, and finally, the waning rate is – although variable by season – identical for all ages. The result is that in the simulations the age-stratified distributions can differ largely in magnitude, but little in shape (right-hand panels in Fig. 5). In reality however, age-specific attack rates differ per season, as the interplay between vaccination and infection histories can affect susceptibility and risk of complications differently in each age group. These age patterns can be captured by considering the different age groups separately per season (Baguelin et al., 2013; Weidemann et al., 2017). Such an alternative analysis shows that the attack rates and immunity levels in each age group are similar to those in the original analysis (SI section 7), although they cannot be used for scenario analyses because of the lack of season-to-season linkage.

Our results show that seasonal influenza vaccination is more effective in averting influenza deaths than influenza infections. This indicates that vaccination mainly works in protecting vaccinees rather than decreasing transmission. A different approach would be to focus vaccination on the transmitters, i.e. children, so as to decrease the infection attack rate and thereby protect the high-risk population indirectly. This paradigm shift has first been explored in Japan (Reichert et al., 2001) and has recently been adopted in the United Kingdom (Pebody et al., 2015) where programmes to vaccinate children in school ages are implemented. Furthermore, this study shows that the impact of the current vaccination progamme is expected to increase over the next decade, despite a projected decrease in the infection attack rate. The vaccination coverage however, was assumed to remain constant per risk and age group, even though actual estimates suggest it is decreasing (Tacken et al., 2015). With the model presented here, it is possible to evaluate modifications to the current vaccination programme, such as a paediatric vaccination programme or a decreasing vaccination coverage in elderly.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.epidem.2018.10.001.

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